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Editorial

This issue of the bulletin has the theme: "First do no harm"- very fundamental principle to medical practice. Risk benefit analysis of therapeutic interventions is very important, yet a difficult task and many at times requires studies of large size with long durations. Application of this principle is met with difficulties not only for new drugs/interventions but also for well-established ones. Continuous updates based on conclusions from recent research findings are need of the hour. The updates and information covered in this issue are believed to help all health care professionals to maximize benefits and minimize the potential harms of the drugs. We are thankful to all readers of previous issues for the encouragement and we hope for constructive feedback from the readers once again.

The Editorial Board

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CGRP Inhibitors in Migraine

Migraine headaches are one of the major contributors to morbidity and disability as a significant proportion of the population is affected by it. Population prevalence studies of migraine report prevalence rates of between 2.6 and 21.7%, globally with an average of ~12%.[1] Migraine can be Common (without aura) or Classical (with aura). Existing treatment options for migraine include ergotamine derivatives, non-steroidal anti-inflammatory drugs (NSAIDs), triptans, antiemetic medications, some calcium channel blockers, and beta-blockers, neuromodulation using devices, and combination therapies. Most of these treatments are unable to provide complete pain relief, have significant adverse effects, and probability of medication overuse.

The exact pathophysiological mechanisms underlying the onset of a migraine attack remain unclear. However, extensive research in the last three decades has demonstrated that calcitonin gene-related peptide (CGRP) plays an important role in the genesis of migraine via the activation of trigeminovascular system. Interestingly, novel prophylactic antimigraine treatments, which directly target CGRP or its receptor, have been explored in the last decade.[2] These novel antimigraine treatments include small molecule CGRP receptor antagonists (gepants); and monoclonal antibodies targeting either CGRP or its receptor.

This is the first category of pharmaceuticals developed as targeted therapy for migraine prevention.[2] The FDA approved drugs in this category are rimegepant, ubrogepant, and atogepant. The monoclonal antibodies against CGRP are eptinezumab, fremanezumab, and galcanezumab whereas the monoclonal antibody against CGRP receptor is available as erenumab.

These new antimigraine drugs, relieve pain and associated symptoms of migraine and prevent or reduce the intensity of migraine attacks by reducing vasodilation and neurogenic inflammation. Moreover, they are effective, well-tolerated, and safer than other drugs that have been used in prophylaxis of migraine.[3]

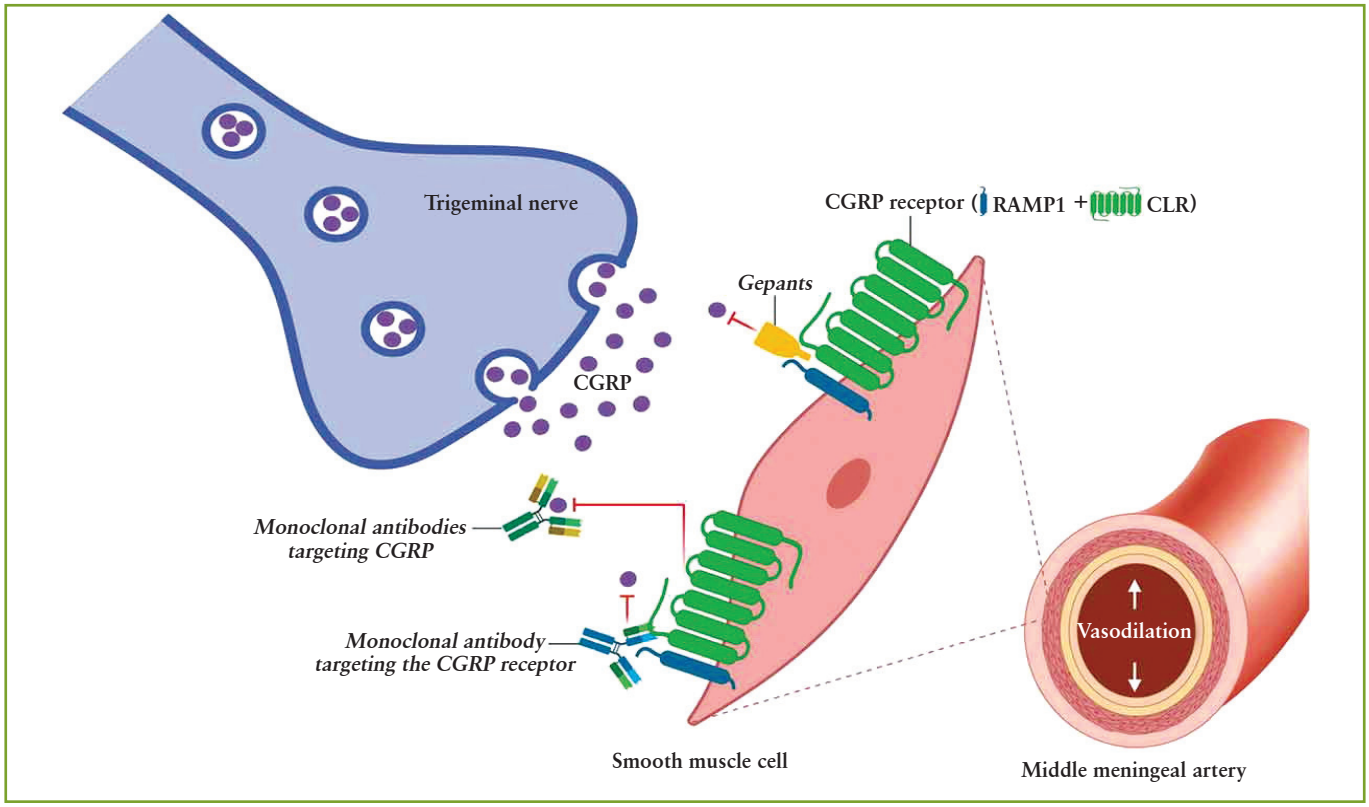

Figure 1: Mechanisms of drugs targeting CGRP[2] (see text for details)

Gepants

These are small molecule CGRP receptor antagonists. These small molecules, which prevent the interaction between CGRP and its receptor (located in the trigeminal ganglion and the vascular smooth muscle cells), can be divided into: (i) first-generation gepants (developed for the acute treatment of migraine); and (ii) second-generation gepants, used for the acute treatment (*i.e.* ubrogepant and rimegepant) and prophylaxis [rimegepant and atogepant] of migraine.

Rimegepant was FDA approved for acute treatment of migraine in February 2020. In Phase II clinical trial, rimegepant in three doses (75, 150, and 300 mg) showed an excellent tolerability profile (similar to that placebo), with no serious adverse effects. The most common adverse effects in the rimegepant-treated patients were nausea (2–8%), vomiting (2–3%), dizziness (2–4%), and urinary tract infection (2–3%). Moreover, since rimegepant produced no cardiovascular adverse effects or hepatotoxicity in the population, it was suggested that this gepant is safe for the treatment of migraine. A recently completed clinical trial for its use in migraine prophylaxis shows that the results are positive but not highly impressive as the difference in reduced number of migraine days per month with rimegepant versus placebo was nominal (-0.8 days).[4]

Atogepant has a higher potency and longer half-life than ubrogepant (used for acute treatment of migraine). A Phase IIb/III randomized, double-blind, placebo-controlled, parallel-group clinical trial evaluated the efficacy, safety, and tolerability of atogepant at different daily (10, 30, or 60 mg) or twice daily (30 or 60 mg) oral doses or placebo during 12 weeks. All active treatment groups showed a significant reduction in their mean monthly migraine/probable migraine headache days (−4.00 for 10 mg; −3.76 for 30 mg; −3.55 for 60 mg; and −4.23 or 4.14 for the twice-daily 30 or 60 mg, respectively) compared to placebo (-2.85 days).[2] Moreover, atogepant was well tolerated with no significant and/or serious side effects. In addition, data obtained from *in vitro* studies using human intracranial and coronary arteries showed that atogepant is more effective and potent in antagonizing CGRP- induced vasodilation in human meningeal arteries as compared with human coronary arteries, suggesting that atogepant would have a safety benefit when considering cardiovascular adverse effects.[5] Results of a phase III clinical trial (NCT03855137 with completion date of 31 August 2021) are awaited.

Conclusion

Based on the advances in basic and clinical research, CGRP has emerged as one of the main targets for the treatment of migraine. In this respect, during the last decades, the development of drugs for the treatment and prophylaxis of migraine has been based on the direct blockade of the CGRP pathway, including either CGRP or the CGRP receptor. The receptor antagonists (gepants) have small molecular sizes and can be administered orally whereas the monoclonal antibodies have a large molecular size and are administered subcutaneously. The monoclonal antibodies are used for prophylaxis and they are expensive

as well. However, that chronic or long-term blockade of the CGRPergic pathway (which has not been explored yet) for the prevention of migraine attacks could cause unwanted (mainly cardiovascular) adverse effects, further studies and Phase IV clinical trials are necessary to further confirm the long-term safety of these new antimigraine drugs.

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Paracetamol Use in Pregnancy and Neurodevelopmental Disorders in Offspring

Paracetamol (acetaminophen) is generally recommended as a safe analgesic and antipyretic during pregnancy. However, recent studies suggest a possible association between paracetamol use in pregnancy and neurodevelopment of offspring.

A Spanish birth cohort study included 2644 mother-child pairs recruited during pregnancy. The proportion of live-born participants evaluated at 1 and 5 years was 88.8% and 79.9%, respectively. The use of paracetamol was evaluated prospectively in two structured interviews. Ever/never use and frequency of use (never, sporadic, persistent) were measured. Main neurodevelopment outcomes were assessed using Childhood Autism Spectrum Test (CAST), Conner's Kiddie Continuous Performance Test (K-CPT), and ADHD-DSM-IV form list. Regression models were adjusted for social determinants and co-morbidities. This study concluded that prenatal paracetamol exposure was associated with a greater number of autism spectrum symptoms in males and showed adverse effects on attention-related outcomes for both genders. These associations seem to be dependent on the frequency of exposure.[1]

A review of nine prospective cohort studies also suggested an association between prenatal paracetamol exposure and the neurodevelopmental outcomes; attention deficit hyperactivity disorder (ADHD), autistic spectrum disorder (ASD), or lower intelligence quotient (IQ). A longer duration of paracetamol use was associated with increased risk. Associations were strongest for hyperactivity and attention-related outcomes. Little modification of associations by indication for use was reported. Together, these nine studies suggested an increased risk of adverse neurodevelopmental outcomes following prenatal paracetamol exposure.[2]

The conclusion of collaborative study of six European population-based birth/child cohorts is similar to the above-mentioned studies. A total of 73,881 mother-child pairs were included in the study. Prenatal and postnatal (up to 18 months) paracetamol exposure was assessed through maternal questionnaires or interviews. ASC and ADHD symptoms were assessed at 4-12 years of age using validated instruments. Children were classified as having borderline/clinical symptoms using recommended cutoffs for each instrument. Hospital diagnoses were also available in one cohort. Analyses were adjusted for child and maternal characteristics along with indications for paracetamol use. Adjusted cohort-specific effect estimates were combined using random-effects meta-analysis. The proportion of children having borderline/clinical symptoms ranged between 0.9 and 12.9% for ASC and between 1.2 and 12.2% for ADHD. Results indicated that children prenatally exposed to paracetamol were 19% and 21% more likely to subsequently have borderline or clinical ASC (OR = 1.19, 95% CI 1.07-1.33) and ADHD symptoms (OR = 1.21, 95% CI 1.07-1.36) compared to non-exposed children. Boys and girls showed higher odds for ASC and ADHD symptoms after prenatal exposure, though these associations were slightly stronger among boys. Postnatal exposure to paracetamol was not associated with ASC or ADHD symptoms.[3]

Another study, which could be the first prospective birth cohort study to examine the association between objective maternal plasma biomarkers of acetaminophen and offspring ADHD diagnosis, and to take into account a large number of potential covariables, analyzed 1180 children enrolled at birth and followed prospectively as part of the Boston Birth Cohort, including 188 with ADHD diagnosis based on electronic medical record review. Maternal biomarkers of paracetamol intake were measured in plasma samples obtained within 1-3 days postpartum. Odds ratios for having ADHD diagnosis or other developmental disorders were estimated using multinomial logistic regression models, adjusting for pertinent covariables. Compared to neurotypical children, significant positive dose-responsive associations with ADHD diagnosis for each maternal paracetamol biomarker was observed. These dose-response associations persisted after adjusting for indication of paracetamol use and other pertinent covariates; and were specific to ADHD, rather than other neurodevelopmental disorders.[4]

Conclusion

Studies highlight the importance of providing clear information to pregnant women about potential risks of paracetamol use in the offspring with specific information on risk of ADHD. Judicious use of paracetamol, keeping the dose and duration to minimum when it is clearly indicated, is justified. As paracetamol is likely to be self-administered by pregnant mothers, regular maternal counseling should include this issue. Non-pharmacological methods of pain management should be considered whenever appropriate and feasible.

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Ivermectin in COVID-19

Ivermectin, a macrocyclic lactone, is an anti-parasitic agent which has been repurposed to use against SARS CoV2 and several clinical trials have shown clinical efficacy mainly in mild to moderate cases. Ivermectin has exhibited antiviral activity against a wide range of RNA and some DNA viruses, for example, Zika, dengue, yellow fever, and others.[1] A large number of studies have been conducted to assess the efficacy of ivermectin treatment among people with COVID-19 and as a prophylaxis among people at higher risk of COVID-19.

Mechanism of action

Ivermectin consists of homolog B1a (≥80%) and B1b (≤20%), homolog B1b is more effective than B1a. Antiviral activity of ivermectin is due to its impact on NF-kB pathway and via binding to the host cell importin alpha/beta1 hetero-dimer, nuclear transport proteins responsible for translocation of various viral species proteins, and these effects in turn also prevent viral replication. Ivermectin homologs can bind with both S1 (the receptor-binding domain of the spike protein) and S2 subunits of the SARS-CoV-2 spike protein (more intense binding) as well as with SARS-CoV-2 main protease, replicase and RNA-dependent RNA polymerase (RdRp). Similarly, ivermectin also found to bind with human transmembrane serine protease 2 (hTMPRSS2) preferably targeting binding zone when S1 protein occupies thereby disrupting host-virus interaction.[2] In silico data have indicated that ivermectin efficiently utilizes viral spike protein, main protease, replicase and hTMPRSS2 receptors as the most possible targets for executing its antiviral efficiency. Therefore, ivermectin exploits protein targets from both virus and human, which could be the reason behind its excellent in vitro efficacy against SARS-CoV-2. [3] Hence, ivermectin may have important utility for the primary prevention of COVID-19 as well in the early stage of viral replication phase of the disease.[3,4]

Comparative in vitro efficacy of ivermectin

Ivermectin possesses a better potential than remdesivir to bind with spike protein receptor binding domain, S2 subunit and RNA dependent RNA polymerase of SARS-CoV-2. However, hydroxychloroquine was found to have the highest binding affinity compared with ivermectin and remdesivir. Ivermectin-hACE2 was inferred as the weakest binding compared with that of hydroxychloroquine and remdesivir. On the other hand, interaction of ivermectin with human transmembrane serine protease 2 (TMPRSS2) was found to be higher than remdesivir but lower to that of hydroxychloroquine. Ivermectin was found to be the best out of the three drugs in binding with viral replicase.[2] As compared with hydroxychloroquine and remdesivir, ivermectin has relatively much higher water solubility and lipophilicity, further, having lesser skin permeation on the other hand.[5]

Effect of ivermectin on inflammatory markers

Effects of ivermectin in reducing inflammatory markers including CRP and d-dimer was significant in mild -moderate patient population on days 7 and 10 of follow- up of ivermectin as compared to control in the metanalysis of randomized trial of ivermectin on SARS-CoV-2. However, variable results were seen with respect to ferritin level.[6]

Effect on viral clearance

Effect of ivermectin on viral clearance was most pronounced in the randomized trials evaluating doses of 0.4mg/kg up to five days. There was a significant difference in time to viral clearance evaluated by polymerase chain reaction (PCR) assays, in favor of ivermectin with mean difference of 3 days. The optimal or maximum effective dose of ivermectin is not yet clear and new trials are evaluating higher doses, up to 1.2mg/kg for 5days.[3,5]

Effect on clinical recovery and duration of hospitalization

Ivermectin demonstrated a shorter duration of hospitalization compared to control with mean difference of 4.27 days. Three of the six trials in meta-analyses showed significantly faster time to clinical recovery as compared to control with mean difference of 1.58 days.[3,5]

Effect on survival

Meta-analysis of 15 trials, assessing 2438 participants, found that ivermectin reduced the risk of death by an average of 62% (95% CI 27%–81%) compared with no ivermectin treatment [average RR (aRR) 0.38, 95% CI 0.19 to 0.73; I2 = 49%]; risk of death 2.3% versus 7.8% among hospitalized patients in this analysis, respectively.[1]

Another meta-analysis of 11 randomized trials with total of 2127 patients, reported 3% death in the ivermectin arms versus 9% death in control arms in cases with mild to moderate severity. However, there was no significant difference in survival between ivermectin and control groups when subgroups with severe symptoms were analyzed.[7,8]

The recently updated WHO therapeutics guidelines included 7 trials and 1419 people in the analysis of mortality. Reporting a risk reduction of 81% (odds ratio 0.19, 95% CI 0.09–0.36), the effect estimate favoring ivermectin was downgraded by 2 levels for imprecision, although the justification for this is unclear as the reported confidence interval is precise (64%–91%).[8]

Adverse effects

Ivermectin is generally well tolerated. Adverse effects may include dizziness, pruritis, nausea, or diarrhea. Neurological adverse effects have been reported with the use of ivermectin for the treatment of onchocerciasis and other parasitic diseases, but it is not clear whether these adverse effects were caused by ivermectin or the underlying conditions. Ivermectin is a minor cytochrome P 3A4 substrate and a p-glycoprotein substrate. Ivermectin is generally given on an empty stomach with water; however, administering ivermectin with food increases its bioavailability.[9]

Precautions and contraindications

Ivermectin binds with GABA receptor in the nervous system. So, it is contraindicated in conditions associated with impaired blood blood-brain barrier e.g., meningitis. Ivermectin is not approved for use in children with less than 15 kg body weight or in pregnant or lactating women (low levels of the drug appear in the mother's milk). This is principally due to concerns about the passage of the drug across the immature blood-brain barrier.[10]

Targeted delivery of ivermectin

Single clinical trial comparing the outcome of 57 patients with mild COVID-19 treated with ivermectin nanosuspension nasal spray twice daily plus the standard treatment and 57 patients treated with the standard treatment concluded that local use of ivermectin mucoadhesive nanosuspension nasal spray is safe and effective in treatment of patients with mild COVID-19 with rapid viral clearance and shortening the anosmia duration.[11]

Conclusion

As oral formulation of ivermectin is cheap, widely available, has known safety profile with multiple trials showing promising outcomes, it may prove to be an important drug in preventing the severity and hospitalizations if started early in symptomatic cases of COVID-19. Unlike expensive options like combination of casirivimab and imdevimab (monoclonal antibodies), ivermectin can contribute significantly in reducing morbidity and mortality in a low to middle income country like Nepal. Results from larger clinical trials such as PRINCIPLE (Platform randomized trial of treatments in the community for epidemic and pandemic illness) being carried out in the United Kingdom will be valuable in making decision for widespread use of ivermectin.[12] Intranasal administration could also be a better option in future. Prospective studies are needed to validate its potential benefit in prevention of SARS-CoV-2 infection as suggested by observational studies that show countries with routine mass drug administration of prophylactic chemotherapy including ivermectin have a significantly lower incidence of COVID-19.

(Note: One clinical trial included in the referred systematic reviews and meta-analyses was retracted for fraudulent data)

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The Janssen COVID-19 Vaccine

The Janssen COVID-19 vaccine has not been approved or licensed by the United States-Food and Drug Administration (US-FDA) but has been authorized by FDA through an Emergency Use Authorization (EUA) for active immunization to prevent COVID-19 in individuals 18 years of age and older.

Mechanism of action

The vaccine consists of a replication-incompetent recombinant adenovirus type 26 (Ad26) vector expressing the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) spike (S) protein in a stabilized conformation. The Ad26 vector expressing the SARS-CoV-2 S protein is grown in PER. C6 TetR cells (cell line derived from human embryonic retinal cells transformed with the Adenovirus Type 5) , in media containing amino acids and no animal-derived proteins. After propagation, the vaccine is processed through several purification steps, formulated with inactive ingredients, and filled into vials. After entering human cells, it expresses the SARS-CoV-2 spike (S) antigen without virus propagation. An immune response elicited to the S antigen protects against COVID-19.

Constituents

Each 0.5 mL dose of Janssen COVID-19 vaccine is formulated to contain 5×10^{10} virus particles and the following inactive ingredients: citric acid monohydrate (0.14 mg), trisodium citrate dihydrate (2.02 mg), ethanol (2.04 mg), 2-hydroxypropyl-β-cyclodextrin (HBCD) (25.50 mg), polysorbate-80 (0.16 mg), sodium chloride (2.19 mg). Each dose may also contain residual amounts of host cell proteins (≤0.15 mcg) and/or host cell DNA (≤3 ng). Janssen COVID-19 vaccine does not contain a preservative. The vial stoppers are not made with natural rubber latex.

Storage and handling

Unpunctured multi-dose vials of the Janssen COVID-19 vaccine should be stored at 2°C to 8°C (36°F to 46°F) It should not be stored frozen and care should be taken to protect from sunlight. Unpunctured vials of Janssen COVID-19 vaccine may be stored between 9°C to 25°C (47°F to77°F) for up to 12 hours. The Janssen COVID-19 vaccine is initially stored frozen by the manufacturer, then shipped at 2°C to 8°C (36°F to 46°F). If the vaccine is still frozen upon receipt, thaw at 2°C to 8°C (36°F to 46°F). If needed immediately it should be thawed at room temperature (maximally 25°C/77°F).

Dosing and schedule

The Janssen COVID-19 vaccine is administered intramuscularly as a **single dose** (0.5 mL).

There are no data available on the use of the Janssen COVID-19 vaccine to complete a vaccination series initiated with another COVID-19 vaccine.

Dose preparation and administration

- The Janssen COVID-19 vaccine is a colorless to slightly yellow, clear to very opalescent suspension Each vaccine vial should be visually inspected for particulate matter and discoloration prior to administration. If either of these conditions exists, it should not be administered.
- Before withdrawing each dose of the vaccine, contents of the multi-dose vial should be carefully mixed by swirling gently in an upright position for 10 seconds. **It should not be shaken.**
- The date and time of first use is to be recorded on the vaccine vial label. After the first dose has been withdrawn,

the vial can be kept between 2° to 8°C (36° to 46°F) for up to 6 hours or at room temperature (maximally 25°C/77°F) for up to 2 hours. It should be discarded if the vaccine is not used within these times.

Contraindication

The Janssen COVID-19 vaccine should not be administered to individuals with a known history of a severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine.

Adverse effects

Thrombosis and thrombocytopenia: Reports of adverse events following use of the Janssen COVID-19 vaccine under emergency use authorization suggest an increased risk of thrombosis involving the cerebral venous sinuses and other sites (including but not limited to the large blood vessels of the abdomen and the veins of the lower extremities) combined with thrombocytopenia and with onset of symptoms approximately one to two weeks after vaccination. **The reporting rate of thrombosis with thrombocytopenia following administration of the Janssen vaccine has been highest in females aged 18 through 49 years; some cases have been fatal.** In individuals with suspected thrombosis with thrombocytopenia following administration of the the vaccine, the use of heparin may be harmful and alternative treatments may be needed. Consultation with hematology specialists is strongly recommended.

Guillain-Barre Syndrome: Reports of adverse events following use of the Janssen COVID-19 vaccine under emergency use authorization suggest an increased risk of Guillain-Barre syndrome during the 42 days following vaccination.

Altered immunocompetence: Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to the Janssen COVID-19 vaccine.

Status in pregnancy

Available data on the vaccine administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

Status in lactation

Data are not available to assess the effects of Janssen COVID-19 vaccine on the breastfed infant or on milk production/ excretion.

Limitations of vaccine effectiveness

The Janssen COVID-19 vaccine may not protect all vaccinated individuals.

Adverse reactions in clinical trials

Adverse reactions reported in a clinical trial following administration of the Janssen COVID-19 Vaccine include injection site pain, headache, fatigue, myalgia, nausea, fever, injection site erythema and injection site swelling. In clinical studies, severe allergic reactions, including anaphylaxis, have been reported following administration of the Janssen COVID-19 vaccine.

Additional adverse reactions, some of which may be serious, may become apparent with more widespread use of the vaccine.

Use with other vaccines

There is no information on the co-administration of the Janssen COVID-19 vaccine with other vaccines.

Source: https://www.janssenlabels.com/emergency-use-authorization/Janssen+COVID-19+Vaccine-HCP-fact-sheet.pdf (Accessed on July 25, 2021)

Article Summary: Proton Pump Inhibitor Use is Associated with Increased Risk of Severity and Mortality from Coronavirus Disease 2019 (COVID-19) Infection. Dig Liver Dis. 2020; 52(12):1410-12.

Introduction

Identification of the risk factors that contribute to the development of severe COVID-19 infections is important to enabling risk stratification, optimizing the hospital resources reallocation, and guiding public health recommendations and interventions. Several medications have been demonstrated to be associated with a reduction in poor outcomes from COVID-19 such as anticoagulant and metformin, while other medications did not alter outcomes of COVID-19 infections such as ACE inhibitors, angiotensin II receptor blocker (ARB), and statins. Proton pump inhibitors (PPIs) are among the very commonly use drugs because of their efficacy in relieving dyspepsia and GERD symptoms and relatively affordable price. In a previous meta-analysis study, it has been shown that the use of proton pump inhibitors (PPIs) may increase the risk of pneumonia even though the heterogeneity of the study is high. Unfortunately, until now, the evidence regarding the link between the use of PPI and COVID-19 outcomes is still conflicting. This article aims to give better evidence for the association between PPI usage and in-hospital outcomes (severity and mortality) of COVID-19 infection.

Methods

A search of the literature was conducted on Google scholar using the keywords "proton pump inhibitors" OR "PPI" OR "clinical characteristics" OR "medications" OR "risk factors" AND "coronavirus disease 2019" OR "COVID-19", between 2019 and present time (September 10th, 2020) with language restricted to English only. The title, abstract, and full text of all articles identified that matched the search criteria were assessed, and those reporting the rate of PPI usage in COVID-19 patients with a clinically validated definition of "severe disease" and "mortality" were included in this meta-analysis. The references of all identified studies were also analyzed (forward and backward citation tracking) to identify other potentially eligible articles.

A meta-analysis was performed using RevMan 5.4 (Cochrane Collaboration) software. Dichotomous variables were calculated using the Mantel-Haenszel formula with random-effects models. The heterogeneity was assessed by using the I^2 statistic with a value of < 25%, 26–50%, and > 50% were considered as low, moderate, and high degrees of heterogeneity, respectively. The effect estimate was reported as risk ratio (RR) along with its 95% confidence intervals (CIs) for dichotomous variables, respectively. *P*-value was two-tailed, and the statistical significance was set at ≤ 0.05.

Results

A total of 7300 records were obtained through systematic electronic searches and other ways. After screening titles, abstracts, and full texts, 6 studies with a total of 5884 COVID-19 patients were included in the meta-analysis. The pooled analysis showed that PPI usage is significantly associated with an increased risk of severe COVID-19 [RR 1.35 (95% CI 1.11–1.63), $p = 0.003$, $I^2 = 45\%$, random-effect modeling] and mortality from COVID-19 infection [RR 1.72 (95% CI 1.02–2.89), $p = 0.04$, $I^2 = 66\%$, random-effect modeling]

Discussion

Based on the pooled analysis of available data, the use of proton pump inhibitors (PPIs) seems to be associated with an enhanced risk of severity and mortality from COVID-19 infection. Several reasons can be proposed to explain this result. Profound hypochlorhydria caused by a PPI can diminish the protective effect of gastric acid. As we know, the ACE2 receptor is also expressed in the mucosa of the gastrointestinal (GI) tract and the fecal-oral route has been raised as one of the potential modes of transmission for COVID-19. Therefore, suppression of gastric acid may increase the survival of SARS-CoV-2 in the stomach and increase the ability of the virus to invade the GI epithelial cells. This condition can increase the viral load which in turn results in a higher chance of developing cytokine storm and severe outcome of the disease. Moreover, the profound hypochlorhydria can also cause an increase in gastric microbiota and small intestinal bacterial overgrowth. The resulting dysbiosis might increase the likelihood of developing enteric infections and sepsis which could complicate the disease. Micro-aspiration of the bacteria may also cause secondary infection in the lungs which may increase the likelihood of developing acute respiratory distress syndrome (ARDS) and severe outcomes of the disease which may increase the mortality rate from COVID-19. PPI can inhibit the enzymatic activity of dimethylarginine dimethylaminohydrolase (DDAH) which will inhibit the nitric oxide synthase with promotion of inflammation and thrombosis, resulting in the development of cardiovascular disease. The idiosyncratic effect of PPIs on the kidneys will also lead to recurrent acute interstitial nephritis, a humoral- and cell-mediated hypersensitivity reaction that results in inflammation of the renal interstitium and tubules. All of these adverse events from PPI can also contribute to the development of severe outcomes and mortality from COVID-19 infection. Finally, PPI can also modulate the immune response by inhibiting neutrophil function. Inhibition of neutrophil function may impair the ability of the body to eradicate the infection and may increase the severity of infection, including COVID-19 infection.

The limitation of this study is that the presence of confounding factors such as patients' age and comorbid conditions that can affect the relationship between PPI use and in-hospital outcome from COVID-19 could not be considered. Moreover, most of the included studies did not mention the information about the type, dose, duration, frequency, and compliance for PPI use. The global RR values of this meta-analysis were also lower than 2.0 which reduces the clinical meaning of the association found. Finally, most of the included studies in this meta-analysis are retrospective cohort design which has limited scientific strength and can only be used to establish an association, but not a causality between PPI use and severity or mortality from COVID-19. However, with this study, PPI usage can further be considered as a matter of concern in COVID-19 patients.

Conclusion

Patients should be more careful when using proton pump inhibitors and only use them if there is a prescription from the doctors. Physicians should be more cautious when prescribing proton pump inhibitors to patients, especially patients with COVID-19, and may consider giving histamine-2 receptor antagonist (H2RA) or antacid instead of PPI for the symptoms of non-severe dyspepsia. For other indications besides dyspepsia, physicians should weigh the potential risk and benefit in each patient when prescribing PPI and may seek alternative treatment. Physicians should also take close monitoring for patients with COVID-19 who have a history of PPI usage to prevent the development of severe outcomes and mortality from the disease. Finally, the use of PPI should be regarded as an important factor in future risk stratification models for COVID-19.

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Safety Profile of Antihistamines

Histamine plays a major role in human health, exerting its diverse effects through four types of receptors.Through the H_1 receptor, histamine is involved in cell proliferation and differentiation, hematopoiesis, embryonic development, regeneration, and wound healing. It is a neurotransmitter, has anticonvulsant activity, and contributes to regulation of the sleep-waking cycle, energy and endocrine homeostasis, cognition and memory.[1,2,3]

Through all 4 known types of histamine receptors, histamine also plays an important role in immune modulation and acute and chronic allergic inflammation.[1,3]

H_1-antihistamines

H_1 antihistamines act as inverse agonists that combine with and stabilize the inactive conformation of the H_1 receptor, shifting the equilibrium toward the inactive state. Currently, the most commonly used classification system is a functional one, in which H_1 antihistamines are classified as either first-generation medications that readily cross the blood-brain barrier and potentially sedate and impair cognitive and psychomotor function, or second-generation drugs that cross the blood-brain barrier to a minimal extent and are relatively nonsedating and do not impair higher mental functions significantly.[1] H_1-antihistamines are widely used in the treatment of allergic and non-allergic disorders.[1,2,3]

Adverse effects of H_1-antihistamines

First-generation H_1 antihistamines

First-generation H_1-antihistamines potentially cause adverse effects in multiple body systems. They have poor selectivity for the H_1-receptor.[1,3] Their main concern, is that even when administered in manufacturers' recommended doses, have the proclivity to interfere with neurotransmission by histamine at CNS H_1 receptors. This potentially leads to adverse CNS symptoms such as sedation (most frequent), drowsiness, somnolence, fatigue, headache, tinnitus, lassitude, blurred vision, diplopia, euphoria, nervousness, insomnia and tremors. [1,2,3] More importantly, it potentially impairs cognitive function, memory, and psychomotor performance. Tolerance to adverse CNS effects does not necessarily occur. After taking one of these older medications at bedtime, some individuals have residual CNS adverse effects the next morning, the so-called antihistamine hangover.[1,2]

Other potential adverse effects, including loss of appetite, nausea, vomiting, epigastric distress and constipation or diarrhea, may be reduced by taking the drug with meals.[2] Adverse effects due to antimuscarinic of first-generation drugs include dryness of mouth and respiratory passages (sometimes cough), urinary retention or frequency and dysuria. Their antiserotonin effects e.g. with cyproheptadine, can cause increased appetite and weight gain. Their anti–α-adrenergic effects include dizziness and orthostatic hypotension.[2,3]

Allergic dermatitis is not uncommon; other hypersensitivity reactions include drug fever and photosensitization. Hematological complications such as leucopenia, agranulocytosis and hemolytic anemia are very rare.[2]

Second-generation H_1 antihistamines

The second generation H_1 antihistamines penetrate poorly into the CNS and thus have a low likelihood of causing CNS effects, although some of them, such as cetirizine and loratadine, potentially cause sedation especially when manufacturers' recommended doses are exceeded. Fexofenadine, is the least sedating of these drugs and is, therefore, considered to be the H_1 antihistamine of choice for airline pilots and people in other safety-critical jobs. The potential cardiac toxicity of H_1 antihistamines that occurs because of blockade of cardiac ion currents, most commonly the IKr current, is not an H_1 antihistamine class effect. The propensity of astemizole and terfenadine to block the IKr current, to prolong the QT interval, and to potentially cause serious polymorphic ventricular arrhythmias such as torsades de pointes is well documented.[4] In addition, some first-generation H_1-antihistamines, such as promethazine, brompheniramine, and diphenhydramine, may also be associated with a prolonged QTc and cardiac arrhythmias when taken in large doses or overdoses.[4] Since withdrawal of regulatory approval for astemizole and terfenadine, the second-generation H_1 antihistamines remaining in use are free from potential cardiac adverse effects. [1,3]

Bilastine, cetirizine, levocetirizine, ebastine, fexofenadine, loratadine, desloratadine, mizolastine and rupatadine have been shown to have excellent safety profile with no evidence of cardiotoxicity even when updosed up to four times their standard licensed dose, provided that the prescribers carefully consider and rule out potential risk factors for cardiotoxicity, such as the presence of inherited long QT syndrome, older age, cardiovascular disorders, hypokalemia and hypomagnesemia, or the use of drugs that either have direct QT prolonging effects or inhibit their metabolism.[5]

Caution is advised for those who are or may become pregnant, as H_1 antihistamines cross the placenta. Though animal studies have shown teratogenic effects, a recent systematic review concluded that antihistamines are unlikely to be strong risk factors for major birth defects. As the drugs are excreted in small amounts in breast milk, first generation antihistamines may cause symptoms like irritability, drowsiness or respiratory depression in the nursing infant.[2]

Antihistamines may have role in immunity as well. A study with clemastine and desloratadine strongly reduced innate responses to *Listeria monocytogenes* in mice as did dexamethasone with overall impaired innate immunity with reduced TNF-α and IL-6 production.[6]

H_1 antihistamine overdoses

After accidental or intentional overdose with a first-generation H_1 antihistamine, CNS symptoms predominate. In adults, these symptoms usually culminate in extreme drowsiness, confusion, and coma; and in the absence of supportive treatment, fatality. In infants and children, paradoxical CNS excitation, with symptoms of irritability, hyperactivity, insomnia, hallucinations, and seizures may occur. Some first-generation H_1 antihistamines also potentially cause dose-related cardiac adverse effects, including sinus tachycardia, reflex tachycardia, supraventricular arrhythmias, and after intentional large overdose, for example, diphenhydramine 0.5 to 1 g, prolongation of the QT interval with ventricular arrhythmias and torsade de pointes has been documented. Massive overdoses of second generation H_1 antihistamines such as cetirizine, fexofenadine, and loratadine have not been causally linked with serious CNS or cardiovascular adverse events or deaths.[1,2,3]

Conclusion

Use of first-generation H_1-antihistamines should generally be discouraged as they are associated with more severe adverse effects which are sometimes serious.The use of antihistamines for reducing symptoms of upper respiratory tract infections may be contributory to immunosuppression leading to prolonged or severe infection.Currently available second-generation H_1-antihistamines are better choice for most of the indications.

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List of Recently Approved Drugs by US Food and Drug Administration (USFDA)

S.N.	Drug	Group/Class	Date of Approval	Indications
1	Viloxazine hydrochloride	Serotonin-norepinephrine modulating agent (SNMA)	April 2, 2021	Treatment of attention deficit hyperactivity disorder (ADHD) in pediatric patients 6 to 17 years of age.
2	Drospirenone and estetrol	Progestin and estrogen combination	April 15, 2021	Contraception.
3	Dostarlimab-gxly	Programmed death receptor-1 (PD-1)–blocking antibody	April 22, 2021	Treatment of women with mismatch repair deficient (dMMR) recurrent or advanced endometrial cancer.
4	Loncastuximab tesirine-lpyl	CD19-directed antibody and alkylating agent conjugate	April 23, 2021	Treatment of adult patients with relapsed or refractory large B-cell lymphoma.
5	Pegcetacoplan	Targeted C3 inhibitor	May 14, 2021	Treatment of paroxysmal nocturnal hemoglobinuria (PNH).
6	Amivantamab-vmjw	Bispecific EGF receptor-directed and MET receptor-directed antibody	May 21, 2021	Treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations.

7	Piflufolastat F 18	Radioactive diagnostic agent	May 26, 2021	Positron emission tomography (PET) of prostate-specific membrane antigen (PSMA) positive lesions in men with prostate cancer.
8	Infigratinib	FGFR tyrosine kinase inhibitor	May 28, 2021	Treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion.
9	Sotorasib	KRASG12C inhibitor	May 28, 2021	Treatment of patients with KRAS G12C-mutated locally advanced or metastatic non- small cell lung cancer (NSCLC), following at least one prior systemic therapy.
10	Ibrexafungerp	Triterpenoid antifungal agent (only non-azole antifungal drug for vaginal candidiasis)	June 1, 2021	Adult and post-menarchal pediatric females with vulvovaginal candidiasis (VVC).
11	Semaglutide	Glucagon-like peptide (GLP-1) receptor agonist	June 4, 2021	As adjunct to diet and exercise for chronic weight management in adult patients who are overweight or obese.
12	Plasminogen, human-tvmh	Plasma-derived plasminogen	June 4, 2021	Replacement therapy for the treatment of patients with plasminogen deficiency type 1 (hypoplasminogenia).
13	Brincidofovir	Nucleotide analog broad-spectrum antiviral	June 4, 2021	Medical countermeasure for smallpox.
14	Aducanumab-avwa	Amyloid beta-directed antibody	June 7, 2021	Patients with mild cognitive impairment or mild dementia stage of Alzheimer's disease.
15	Asparaginase erwinia chrysanthemi (recombinant)-rywn	Asparagine specific enzyme	June 30, 2021	A component of a multi-agent chemotherapeutic regimen for the treatment of acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL).
16	Finerenone	Non-steroidal, selective mineralocorticoid receptor antagonist (MRA)	July 9, 2021	Treatment of patients with chronic kidney disease (CKD) associated with type 2 diabetes (T2D).
17	Belumosudil	Kinase inhibitor	July 16, 2021	Treatment of patients with chronic graft-versus-host disease (cGVHD).
18	Fexinidazole	Nitroimidazole antibacterial	July 16, 2021	Treatment of human African trypanosomiasis (African sleeping sickness) due to Trypanosoma brucei gambiense in patients 6 years of age and older and weighing at least 20 kg.
19	Odevixibat	Ileal bile acid transport (IBAT) inhibitor	July 20, 2021	Treatment of pruritus in patients 3 months of age and older with progressive familial intrahepatic cholestasis (PFIC).
20	Anifrolumab-fnia	Type I interferon (IFN) receptor antagonist	July 30, 2021	Treatment of adult patients with moderate to severe systemic lupus erythematosus (SLE), who are receiving standard therapy.

Source: https://www.drugs.com/newdrugs.html

FINERENONE

Finerenone is a third-generation non-steroidal mineralocorticoid receptor antagonist with stronger mineralocorticoid receptor-binding potential compared with spironolactone and eplerenone. The FDA approval on 9 July 2021 was based on the results from the phase 3 FIDELIO-DKD trial, which demonstrated positive kidney and cardiovascular outcomes in patients with CKD associated with T2D.[1,2]

Finerenone is a white to yellow crystalline powder. It is practically insoluble in water; and sparingly soluble in 0.1 M HCl, ethanol, and acetone.[2] Patients with kidney disease, would originally be given spironolactone or eplerenone to antagonize the mineralocorticoid receptor.[3] Spironolactone has low selectivity and affinity for the receptor; it dissociates quickly and can also have effects on the androgen, progesterone, and glucocorticoid receptors. Eplerenone is more selective and has longer-lasting effects.6 More selective nonsteroidal mineralocorticoid antagonists such as apararenone, esaxerenone, and finerenone were later developed.[1-3]

Pharmacokinetics [2,3]

Finerenone exposure increased proportionally over a dose range of 1.25 to 80 mg (0.06 to 4 times the maximum approved recommended dosage). A steady-state of finerenone was achieved after 2 days of dosing.

Absorption: Finerenone is completely absorbed after oral administration but undergoes metabolism resulting in absolute bioavailability of 44%. Finerenone Cmax was achieved between 0.5 and 1.25 hours after dosing.

Effect of Food: There was no clinically significant effect on finerenone AUC following administration with high fat, high calorie food.

Distribution: The volume of distribution at steady-state (Vss) of finerenone is 52.6 L. Plasma protein binding of finerenone is 92%, primarily to serum albumin, in vitro.

Elimination: The terminal half-life of finerenone is about 2 to 3 hours, and the systemic blood clearance is about 25 L/h.

Metabolism: Finerenone is primarily metabolized by CYP3A4 (90%) and to a lesser extent by CYP2C8 (10%) to inactive metabolites.

Excretion: About 80% of the administered dose is excreted in urine (<1% as unchanged) and approximately 20% in feces (< 0.2% as unchanged).

Mechanism of action

Finerenone is a nonsteroidal, selective antagonist of the mineralocorticoid receptor (MR), which is activated by aldosterone and cortisol and regulates gene transcription. Finerenone blocks MR mediated sodium reabsorption and MR overactivation in both epithelial (e.g., kidney) and nonepithelial (e.g., heart, and blood vessels) tissues. MR overactivation is thought to contribute to fibrosis and inflammation. Finerenone has a high potency and selectivity for the MR and has no relevant affinity for androgen, progesterone, estrogen, and glucocorticoid receptors.[1,3]

Indication

It is indicated to reduce the risk of sustained eGFR decline, kidney failure, cardiovascular death, non-fatal myocardial infarction (MI) and hospitalization for heart failure in adult patients with chronic kidney disease (CKD) associated with type 2 diabetes (T2D).[1]

Dosage forms & strengths

10mg tablet, film coated

Recommended starting sosage

eGFR (mL/min/1.73m^2)	Starting Dose
≥ 60	20 mg once daily
≥ 25 to < 60	10 mg once daily
< 25	Not recommended

Measure serum potassium levels and estimated glomerular filtration rate (eGFR) before initiation. Do not initiate treatment if serum potassium is > 5.0 mEq/L.

Measure serum potassium 4 weeks after initiating treatment and adjust dose; if serum potassium levels are > 4.8 to 5.0 mEq/L, initiation of finerenone treatment may be considered with additional serum potassium monitoring within the first 4 weeks based on clinical judgment and serum potassium levels Monitor serum potassium 4 weeks after a dose adjustment and throughout treatment and adjust the dose as needed. [2-4]

		10 mg once daily	**20 mg once daily**
Current Serum Potassium (mEq/L	≤ 4.8	Increase the dose to 20 mg once daily.*	Maintain 20 mg once daily.
	> 4.8 – 5.5	Maintain 10 mg once daily.	Maintain 20 mg once daily.
	> 5.5	Withhold. Consider restarting at 10 mg once daily when serum potassium ≤ 5.0 mEq/L.	

* If eGFR has decreased by more than 30% compared to previous measurement, maintain 10 mg dose.

Adverse effects[2,3]

Hyperkalemia hypotension and hyponatremia are the reported major adverse effects of finerenone.

Pregnancy**:** There are no available data on finerenone use in pregnancy to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.

Animal studies have shown developmental toxicity at exposures about 4 times those expected in humans.[2, 3]

Lactation**:** Avoid breastfeeding during treatment and one day after treatment is stopped.

Drug interactions

Administration of finerenone with strong inhibitors of CYP3A4 (such as clarithromycin, itraconazole, ketoconazole, voriconazole, posaconazole, voriconazole, ritonavir, lopinavir, cobicistat) should be avoided. Administration of finerenone with moderate and weak inhibitors of CYP3A4 (such as amiodarone, erythromycin, fluconazole, diltiazem, verapamil, conivaptan) should only be used under medical supervision so that potassium levels can be monitored and dosages adjusted if needed.[3,5]

Food interactions

Avoid grapefruit products. Grapefruit products may increase exposure to finerenone, increasing the risk and severity of adverse effects. It can be taken with or without food. Food does not have a clinically significant effect on the area under the curve.[2]

Conclusion

Finerenone is a non-steroidal mineralocorticoid receptor antagonist indicated to lower the risk of eGFR decline, end-stage kidney disease, cardiovascular death, heart attack, and hospitalization for heart failure in chronic kidney disease associated with type 2 diabetes.

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Hyperinsulinemic Euglycemic Therapy (HIET) for Beta Blocker and Calcium Channel Blocker Toxicity

Beta-blocker (BB) or calcium channel blocker (CCB) toxicity is potentially lethal because of cardiogenic shock. CCB overdose is generally associated with higher mortality rates in comparison to other cardiovascular drug overdoses.[1]

Mechanism of toxicity [2]

Overdose with BB leads to decreased myocardial activity, triggering bradycardia and decreasing contractility. Toxic effects of CCBs are primarily due to conduction blockade and reduced contractility of myocardial cells and vasodilatation. Calcium channel blockers also block L-type calcium channels in the peripheral vasculature. This can lead to shock due to a large drop in blood pressure caused by excessive vasodilation. The situation can further deteriorate because CCBs also inhibit the myocardial compensatory effects of increased heart rate (HR) and contractility. Outside of the cardiovascular system, blockade of L-type calcium channels in pancreatic β cells can result in decreased release of insulin. Patients can potentially experience hyperglycemia in a severe CCB overdose due to inhibition of insulin secretion. In addition, resulting hypoinsulinemia is thought to play a major role in CCB overdose. Myocardial cells primarily oxidize fatty acids as a source of energy. During periods of stress, the cardiac cells begin using glucose as their main energy source. Because of the hypoinsulinemia and insulin resistance from a CCB overdose, myocardial cells are unable to use glucose freely for energy This further decreases contractility of the heart, leading to shock. The combination of decreased cardiac function, vasodilation, and inability to use glucose due to hypoinsulinemia can explain why CCB overdose has the potential to be so deadly and why proper management of this condition is important.

Conventional management[2]

Initial assessment is directed to establish whether or not pharmacologic intervention is necessary for patients who have ingested potentially toxic doses of BBs or CCBs. Signs and symptoms of toxicity often include decreased heart rate, blood pressure, and/or altered mental status. Patients may present with electrocardiogram (ECG) abnormalities such as sinus bradycardia, atrioventricular block, or QTc prolongation. For patients who are asymptomatic, observation without pharmacologic intervention is often recommended. Activated charcoal may be considered early on in the treatment of CCB and BB overdose to inhibit further absorption.

Conventional pharmacologic therapy has included glucagon, calcium, positive inotropes, and vasopressor agents. Intravenous fluids are often recommended as the initial intervention in both BB and CCB toxicity. Along with IV fluids, 3–4 doses of IV calcium chloride 10% (0.2 ml/kg) or gluconate 10% (0.6 ml/kg) are often administered in a CCB overdose. Glucagon (0.05–0.15 mg/kg bolus followed by 0.05–0.1 mg/kg/hr) is recommended in BB toxicity. Intravenous lipid emulsion therapy has been theorized to be a useful strategy in cases of toxicity caused by lipophilic agents.

Mechanisms of HIET[2]

Although the exact mechanism of HIET has not been defined, animal models provide its theoretical basis. Figure 2 illustrates the proposed mechanisms of HIET that treat BB and CCB toxic effects. Administering high-dose insulin therapy allows myocardial cells to uptake and effectively exploit glucose as a source of energy. Insulin also has direct concentration-dependent inotropic effects on human myocardial cells.

Recommended approach for HIET in CCB and BB overdose [2]

Indications for initiation: Patients who have ingested potentially toxic amounts of BB or CCB medications who are symptomatic and in whom an increase in myocardial function is desired. Symptoms may include decreased HR and/or BP. Symptomatic patients may also experience abnormalities in peripheral vascular resistance or altered mental status. Patients may present with ECG abnormalities such as sinus bradycardia, AV block, or QTc prolongation.

Regular insulin IV bolus: Administer 1 unit/kg as a single bolus dose.

Regular insulin IV infusion: Initiate infusion at 0.5–1 unit/kg/hr. Titrate upward every 10–15 min to clinical response. Reasonable maximum dose: 10 units/kg/hr.

Maintain euglycemia: Administer continuous dextrose infusion concomitantly with regular insulin infusion to maintain blood glucose (BG) concentration > 100 mg/dl. Immediate dextrose supplementation may not be necessary in severe CCB overdose due to insulin resistance; check initial BG concentration in these patients and hold dextrose if BG ≥ 200 mg/dl. Initiate dextrose at 0.5 g/kg/hr. Concentrations ≥ 20% dextrose administered via central line may be preferred to prevent fluid overload.

Efficacy targets: No consensus on ideal efficacy targets in published literature. Reasonable to target a systolic BP ≥ 90 mm Hg and HR ≥ 50 bpm. If present at baseline, abnormalities in mental status and ECG readings should resolve.

Consider potassium supplementation: Administer IV potassium supplementation as needed to maintain serum potassium concentrations ≥ 3 mEq/L.

Monitoring parameters: Continually monitor vital signs and symptoms of overdose including HR, BP, mean arterial pressure, signs of adequate perfusion, and mental status changes. Monitor BG every 15–60 min. Monitor serum potassium every hour upon therapy initiation, then every 60–120 min once stable. Monitor serum electrolytes such as magnesium and phosphorous hourly, then every 4–6 hrs once patients are stable. Serial ECG monitoring until patients stabilize may be beneficial for those with abnormalities at initial presentation.

Duration of therapy: Reasonable to continue HIET until hemodynamic stability is achieved and patient is stable. Therapy should be slowly tapered off over a period of at least several hours. Continually monitor for worsening BP, HR, or mental status as therapy is discontinued. Consider continuing dextrose for several hours after weaning insulin to avoid hypoglycemia.

Adverse effects

Most common adverse effects of HIET include hypoglycemia and electrolyte imbalances, especially hypokalemia. It is important to note that hypoglycemia may occur up to several hours after the insulin infusion has been completed.[2] HIET has been shown to have promising efficacy and safety in several pediatric case reports too.[3]

Conclusion

HIET in BB and CCB overdose involves administration of high-dose insulin while maintaining normal serum glucose concentrations. HIET can be very effective in the management of CCB and BB overdose when it is refractory to initial therapy of IV fluids, IV calcium (in CCB overdose), or glucagon (in BB overdose). HIET appears to be safe, provided patients are stringently monitored.[2] However, there is need to overcome barriers in utilization of HIET protocols to improve patient outcome.[4]

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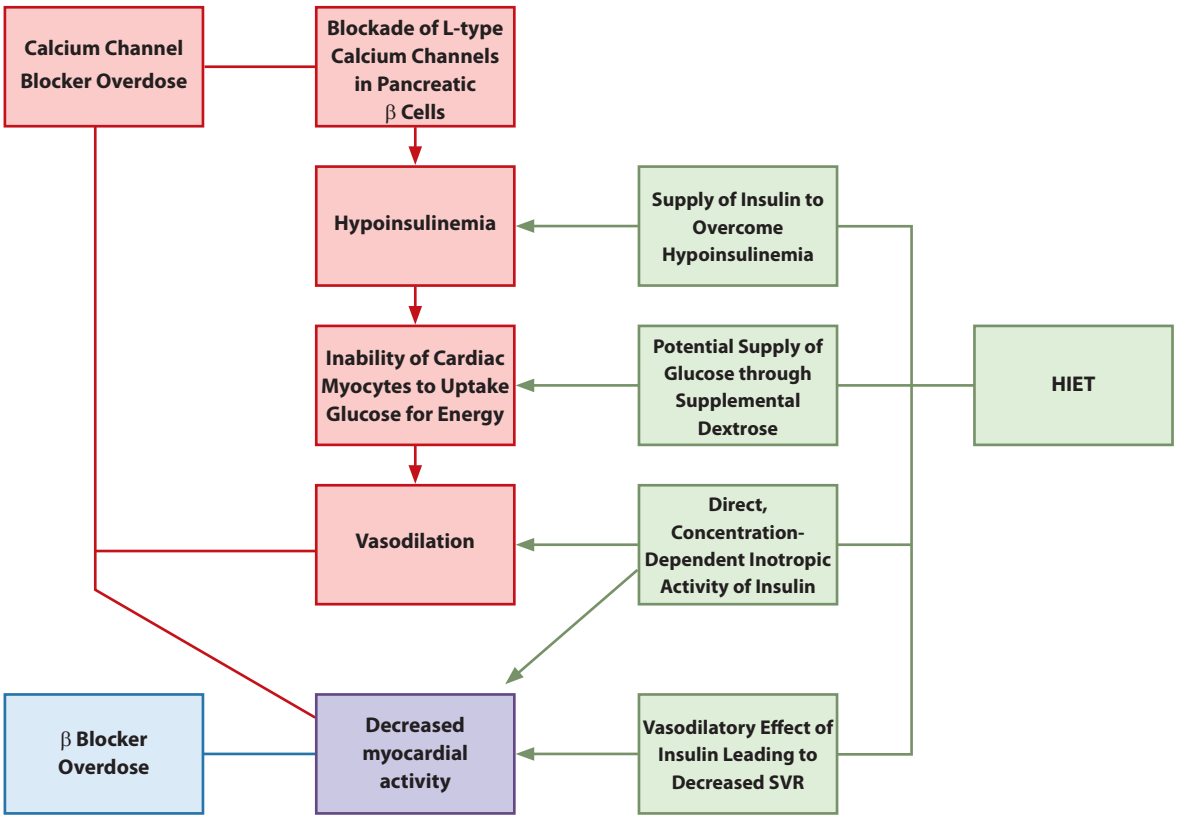

Figure 2: Proposed hyperinsulinemic-euglycemic therapy (HIET) mechanisms.[2] SVR = systemic vascular resistance.

KEY MESSAGES OF THE ISSUE

1. Migraine headaches are one of the major contributors to morbidity and disability as significant proportion of the population is affected by it. Existing treatment options for migraine include ergotamine derivatives, non-steroidal anti-inflammatory drugs (NSAIDs), triptans, antiemetic medications, some calcium channel inhibitors and beta blockers, neuromodulation using devices and combination therapies. Extensive research in the last three decades has demonstrated that calcitonin-gene related peptide (CGRP) plays an important role in the genesis of migraine via the activation of trigeminovascular system. Interestingly, novel prophylactic antimigraine treatments, which directly target CGRP or its receptor, have been explored in the last decade. These novel antimigraine treatments include: (i) small molecule CGRP receptor antagonists (gepants); and monoclonal antibodies targeting either CGRP or its receptor.
2. Paracetamol (acetaminophen) is generally recommended as a safe analgesic and antipyretic during pregnancy. However, recent studies suggest a possible association between paracetamol use in pregnancy and neurodevelopment of offspring: attention deficit hyperactivity disorder (ADHD), autistic spectrum disorder (ASD), or lower intelligence quotient (IQ) to name some. These study-results highlight the importance of providing clear information to pregnant women about potential risks of paracetamol use in the offspring with specific information on risk of ADHD and minimizing the exposure by keeping the dose and duration to minimum when it is required.
3. Ivermectin, an antiparasitic drug used worldwide for a broad number of parasites has been investigated for repurposing against SARS-CoV-2. Antiviral activity of ivermectin has been demonstrated recently for SARS-CoV-2. Antiviral activity of ivermectin is due to its impact on NF-kB pathway and via binding to the host cell importin alpha/beta1 heterodimer, nuclear transport proteins responsible for translocation of various viral species proteins preventing viral replication. It has been shown to reduce inflammatory markers, achieve viral clearance more quickly and improve survival compared with standard of care in COVID-19 patients with mild to moderate severity. It may prove to be an important drug in preventing the severity and hospitalizations if started early in symptomatic cases of COVID-19.
4. The Janssen COVID-19 Vaccine has been authorized by FDA through an Emergency Use Authorization (EUA) for active immunization to prevent Coronavirus Disease 2019 (COVID-19) in individuals 18 years of age and older. The vaccine consists of a replication-incompetent recombinant adenovirus type 26 (Ad26) vector expressing the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) spike (S) protein in a stabilized conformation. After entering human cells, it expresses the SARS-CoV-2 spike (S) antigen without virus propagation. An immune response elicited to

the S antigen protects against COVID-19. The Janssen COVID-19 vaccine is administered intramuscularly as a single dose (0.5 mL). Serious adverse effects reported with this vaccine are thrombosis, thrombocytopenia and Guillain-Barre syndrome (GBS).

5. The results of a recent meta-analysis show that protom pump inhibitor(PPI) usage is significantly associated with an increased risk of severe COVID-19 and mortality from COVID-19 infection. Therefore, physicians should avoid use of PPI as far as possible in such patients and monitor patients with COVID-19 who have a history of recent PPI usage to prevent the development of severe outcome and mortality from the disease.
6. First -generation H_1 antihistamines readily cross the blood brain barrier and potentially sedate and impair cognitive and psychomotor function. In contrast, the second-generation medications are relatively free from adverse effects, including CNS and cardiac toxicity, when administered in standard doses and even if taken in overdose. Immunosuppression by antihistamines may be important factor to consider while treating upper respiratory tract infections.
7. Finerenone is the only non-steroidal mineralocorticoid receptor antagonist to be US-FDA approved. It is used in the treatment of patients with chronic kidney disease (CKD) associated with type 2 diabetes (T2D). It is essential to measure serum potassium levels and estimated glomerular filtration rate (eGFR) before initiation and during monitoring of drug effect.
8. Hyperinsulinemic euglycemic therapy (HIET) in beta blocker(BB) and calcium channel blocker (CCB)overdose involves administration of high-dose insulin while maintaining normal serum glucose concentrations. HIET can be very effective in the management of CCB and BB overdose when it is refractory to initial conventional therapy. HIET appears to be safe, provided patients are stringently monitored for hypoglycemia and hypokalemia.

Patient-related services provided by Department of Pharmacology, College of Medicine, NAIHS

1. **Plasma cholinesterase estimation at SBH**
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   Drug and therapeutics-related questions are answered from the department.
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Please send your comments, suggestions and contributions for upcoming issues on the following address:

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